REMARKS

Applicant wishes to direct the Examiner's attention to co-pending applications and patent owned by the assignee: 11/367,609 (Patent No. 7,439,324); 11/565,967; 11/682,217; 11/850,502 and 12/236,731.

By the present amendment, claims 1 and 17 have been amended as described below and claims 3-8, 18, 19, 23, 27, 31-38, 40, 42-46 and 50 have been provisionally withdrawn from consideration.

The amendments to the claims have been made without prejudice. Applicant reserves the right to pursue any of the deleted subject matter in a further divisional, continuation or continuation-in-part application. This Amendment does not contain new matter.

The Office Action dated December 23, 2008 has been carefully considered. It is believed that the claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Status of Application/Election/Restrictions

Applicant maintains that the restriction based on Kim et al. is erroneous and should be withdrawn and that all claims should be rejoined in this prosecution. Kim et al. teaches using a detection agent (e.g. an anti-synuclein antibody) to detect both wild type and non-wildtype (e.g. alpha-synuclein aggregated by hydroxyl radical). Accordingly, the target epitope is accessible in both wild type (e.g. unaggregated) and non-wildtype alpha-synuclein in contrast to the instant claims. Kim et al. also teaches using a detection agent (e.g. anti-DNP antibody) to detect a multitude of created epitopes (e.g. DNPH modified carbonyl groups). Contrary to the instant claims, the DNPH modified epitope in Kim et al., e.g. the DNPH modified carbonyl groups, is not accessible in one conformation and inaccessible in another since it is only present in one conformation. This is true even if the Examiner is alleging that the carbonyl group is considered the epitope – the carbonyl group is not present in the wildtype conformation of alpha-synuclein and therefore cannot meet the limitations of the present claims.

While the present application describes a method of detecting the conformation of alpha-synuclein (the same protein discussed in Kim et al.), the claimed method is different that the invention described by Kim et al. In the claimed method, the blocking agent reacts specifically with accessible epitopes in the wildtype conformation synuclein protein. The target epitope is inaccessible in the non-wildtype conformation. Detection of the non-wildtype conformation is made by detecting target epitope that was protected from the blocking agent. See, e.g., Example 10. In contrast, Kim et al. detects the epitope that was modified by the blocking agent. Accordingly, Applicant respectfully submits that the unifying feature of the claimed method is detecting whether a candidate polypeptide is in a wildtype conformation or non-wildtype conformation by using a detection agent that binds a target epitope that was converted from an inaccessible target epitope, to an accessible target epitope.

In light of the above, Applicant respectfully requests that the non-elected claims be rejoined.

Specification Objections

The Examiner has objected to the specification because it contains embedded hyperlinks at pages 6 and 7. Applicant has deleted the embedded hyperlinks as required by the Examiner.

The Examiner alleges the title of the application is not descriptive indicating that the elected invention is directed to detecting prion. Applicant respectfully submits that the elected species is prions; however, the generic claim of the elected invention is not so limited. Applicant has amended the title to read "Detection of pathogenic polypeptides using an epitope protection assay".

Claim Objections

The Examiner has objected to claims 3-8, 18, 19, 23, 27, 31-38, 40, 42-46 and 50 alleging that the status of these claims is not correct because these claims are withdrawn from consideration. As required by the Examiner, Applicant has indicated that these claims are withdrawn. However, this is done provisionally, pending the Examiner's further consideration of Applicant's traversal of the restriction requirement in this response.

In addition, Applicant has amended claim 1 to replace "removing unreacted blocking agent" with "removing the unreacted blocking agent" as required by the Examiner. The Examiner has also objected to claim 17 because the recitation "6H4 or 3F4" is not an antibody molecule. Although Applicant respectfully disagrees, Applicant has amended claim 17 to recite "the antibody comprises the antibody designated as 6H4 or the antibody designated as 3F4" to speed prosecution. Applicant has also replaced the comma at the end of claim 17 with a period to correct this typographical error.

In light of the above, Applicant respectfully requests the objections to these claims be withdrawn.

35 USC § 112, second paragraph

The Examiner has rejected claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 as indefinite alleging the language recited in the independent claims does not make sense. The Examiner alleges that the claims are directed to detecting whether a candidate polypeptide including the target epitope is in a wildtype or non-wildtype conformation but that the claim language also encompasses a step to modify a polypeptide. The Examiner alleges the step of modifying a polypeptide itself would have changed a wildtype polypeptide to a non-wildtype polypeptide and thus would have resulted in a polypeptide in a non-wildtype conformation. Although Applicant disagrees since the claim clearly states "wherein binding... indicates that the candidate polypeptide was in a" non-wildtype or wildtype conformation, indicating that the method is drawn to determining the conformation of the candidate polypeptide before application of the method, Applicant has amended claim 1 to read "A method of detecting whether a candidate polypeptide including a target epitope is in i) a wildtype conformation or ii) a non-

wildtype conformation in a sample, comprising" and further adding "in the sample" to the end of the claim to reiterate that the conformation of the candidate polypeptide sought to be determined is its conformation prior to contacting it with blocking agent, e.g. its conformation state in the sample. To the extent that the amendment does not address the Examiner's concern, Applicant respectfully disagrees.

The methods are directed to detecting the conformation of candidate polypeptides that can exist in at least two different conformations. The claimed methods are very useful for screening samples for the presence of disease proteins that, for example, are the aggregated forms of normal proteins, such as aggregated Abeta protein indicating Alzheimer's disease, aggregated PrP protein indicating mad cow disease, aggregated SOD protein indicating ALS disease, etc.

In testing for an aggregated form of a target protein, the sample is first treated so that blocking groups are fixed to exposed protein surfaces. This prevents binding of the affinity probe that would normally bind these surfaces. Only exposed surfaces are "blocked", however, so that dissociation of the non-wildtype polypeptide effectively releases protein surfaces that, because they were protected from the blocking reaction, remain reactive with the affinity probes. A sample testing positive for the affinity probes after blocking and dissociation is a sample containing an aggregated form of the target protein.

In claim 1 as presented, the step of "modifying the candidate polypeptide to convert any inaccessible target epitope to accessible target epitope" is exemplified by the use of dissociating conditions to convert aggregated protein to component protein. In this step, target epitopes on the component protein that were insulated from the blocking reaction are exposed when released from their aggregated state. The same conversion step could be performed on a monomeric protein, simply by adjusting conditions so that the monomeric protein converts from a disease (non-wildtype) conformation to a normal (wildtype) conformation, thus shifting its reactivity to affinity probes, such as antibodies.

In the terminology of claim 1, the component protein is the wild type conformation, and the aggregated protein is the non-wild type conformation. So, the step of converting from non-wildtype to wildtype is performed, in one example, by dissociating and/or denaturing to convert aggregated protein to component protein.

With specific reference to the present claims, the method entails the steps of introducing a blocking agent that will block the target epitope only if it is accessible to the blocking agent, i.e.,

> "*contacting the polypeptide with a blocking agent that selectively blocks accessible target epitope, wherein in the wildtype conformation, the target epitope is accessible and reacts with the blocking agent, and wherein in the non-wildtype conformation, the target epitope cannot react with the blocking agent*;

To determine if that target epitope in fact was blocked or not by reaction with the blocking agent, conditions are then modified resulting in a conformational shift in which target epitope becomes accessible.

> "*removing the unreacted blocking agent from contact with the polypeptide;*
> *modifying the candidate polypeptide to convert any inaccessible target epitope to accessible target epitope; and ...*"

Antibody (or other binding detection agent) is then used to determine if the target epitope is now available for binding. If the probe binds, then the target epitope must have been inaccessible during the blocking reaction, indicating that an abnormal form of the protein is present, and that a disease state is indicated, i.e.,

> "*contacting the polypeptide with a detection agent that binds selectively to the target epitope that was converted from inaccessible target epitope to accessible target epitope, wherein binding between detection agent and converted target epitope indicates that the candidate polypeptide was in a non-wildtype conformation and wherein lack of binding between the detection agent and the target epitope indicates that the polypeptide was in a wildtype conformation in the sample.*"

Accordingly Applicant respectfully submits that the claims are not indefinite. In light of the above, Applicant respectfully requests that the objection to claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 be withdrawn.

The Examiner has rejected claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47, 49 and 51 as being incomplete for omitting essential steps. With respect, it is submitted that the rejected claims each recite all of the elements essential to the operation of the claimed methods. The conversion step is dependent on the nature of the protein analyte, and the differences in conformational states that define the protein as either wildtype or non-wildtype, e.g., disease type. The claimed method is not limited in principle to the particular means by which this conversion is accomplished. As noted in the specification, a target epitope that is inaccessible in protein that is presented as an aggregate in the disease state can be converted to an accessible target epitope simply by denaturation or dissociation, as set out in claims 10-14. Inaccessible target epitopes in proteins that, in their disease form, are not aggregated but instead present simply with an altered conformation in their monomeric state can be converted to accessible target epitopes also by altering conditions, such as by alteration of pH, tonicitiy, temperature, etc. (e.g. wherein the target epitope is accessible similar to the wildtype protein). The particular treatment will be known or be determinable for each of the disease proteins targeted for detection in the assay. Furthermore, the present specification teaches useful probes and conversion conditions for a wide variety of proteins, as set out for instance in the Table on page 39 and in the examples.

Moreover, the claimed method is not limited to the particular type of affinity probe chosen to detect the presence of protein converted to the wildtype state. As recited in claim 1, the protein is one that presents a target epitope, and is identified using a "detection agent" that binds that epitope. The nature of the detection agent is not critical to the operation of the assay. The binding agent is optionally an antibody, although binding fragments thereof and aptamers can also be used, as noted in the specification.

In light of the above, Applicant respectfully requests that the objection to 35 USC § 112, second paragraph be withdrawn.

35 USC § 112, first paragraph

The Examiner has rejected claim 17 as failing to comply with the enablement requirement. Specifically, the Examiner alleges the claimed method employs biological materials that are not readily available to the public.

Applicant respectfully disagrees. The antibodies 6H4 and 3F4 are commercially available antibodies. The 3F4 antibody was deposited for patent purposes as ATCC HB 9222, as described in U.S. Patent No. 4,806,627. The 6H4 antibody was also deposited for patent purposes as DSM ACC2295, as described U.S. Patent No. 6,765,088. These antibodies, thus, are on deposit and were available to the public before the filing date of the present application.

The Examiner has rejected claims 1-2, 9-17, 20-22, 29-30, 39-41, 47-49 and 51 alleging the specification does not reasonably provide enablement for the claimed method of detecting whether a structurally and functionally defined candidate polypeptide with an unknown target epitope is in a wildtype or non-wildtype conformation by using an unknown blocking agent to block an unknown accessible epitope in the polypeptide, modifying and determining whether the modified mutant is a wildtype or non-wildtype conformation as broadly claimed.

Applicant respectfully disagrees. Applicant respectfully submits that the many teachings of the disclosure and knowledge in the prior art support the breadth claimed. Further, Applicant specifically disagrees with the Examiner's characterization of the nature of the claimed method. In one embodiment, Applicants show that a model prion, which is made by acid treating wildtype PrP (non-disease conformation), that resembles the characteristics of PrP^{Sc} (e.g. disease conformation) is incubated with the blocking agent peroxynitrite and then subjected to immunoblotting (e.g. which involves modifying the candidate polypeptide by denaturation). The model prion is recognized by two different detection agents (3F4 and 6H4 antibodies). This shows that the disease like model prion PrP is protected from modification by peroxynitrite such that target epitopes become accesible when modified (e.g. denatured during immunoblot procedure) to detection by the detection agents. Applicant shows that the epitope protection phenomenon shown from model proteins is also observed in authentic disease misfolded prion protein in Scrapie infected hamster brain. In Example 4, Applicants further describe experiments

with various binding agents including peroxynitrite, hydrogen peroxide and methylene and describe how to optimize parameters of the assay. They further provide teaching for adapting the assay to a fluorescent ELISA system in Example 5. Example 8 shows similar detection of amyloid B using the EPA technology and Example 9 provides instruction for modifying SOD1 by succinic anhydride and/or DEPC and teaches this property can be exploited to discriminate between aggregated and unaggregated SOD1 protein. Specific factors are also given in Example 9 for selecting antibodies that have utility for detecting aggregated SOD1 using the assay. Aggregated alphasynuclein is detected in Example 10. This Example teaches that SYN-1 is optionally blocked by chemical modification by DEPC which is histidine reactive and alpha-synuclein that is aggregated in vitro is protected from modification by DEPC where normal protein is not. A number of additional examples are provided.

Further, Applicant discloses a number of different possible blocking agents including peroxynitrite, methylene, hydrogen peroxide, diethylpyrocarbonate, 4-hydroxynonenal epoxides and diazirine (see page 25, blocking agent definition). Applicant respectfully submits that a person skilled in the art would readily be able to determine relevant blocking agents that function as claimed, as well as detection agents that are suitable for use with the methods presently claimed.

Accordingly, the Examiner's characterization of the nature of the invention is unduly limited. Applicant respectfully submits that Applicant has identified a novel method of determining the conformation of polypeptides that can exist in at least two conformations, e.g. in aggregated or non-aggregated conformations. Given the wide breadth of the applicability of such a method, Applicant respectfully submits Applicant is entitled to the present breadth of claims claimed.

Applicant also disagrees with the Examiner's characterization of the prior art/predictability and experimentation.

The Examiner alleges on page 10 that independent claims 1, 39 and 49 encompass use of structurally and functionally undefined polypeptides, structurally and functionally undefined

target epitopes, inaccessible and accessible target epitopes and encompass use of structurally and functionally undefined blocking agents and detection agents. As described above, the application discloses and provides exemplary support for detecting the conformation of several unrelated polypeptides, several unrelated target epitopes using several unrelated blocking agents and detection agents, supporting a wide breadth of claims. Contrary to the Examiner's assertion, the group of polypeptides claimed are defined to be polypeptides that exist in a wild-type and non-wildtype conformation and the group of target epitopes claimed are defined to be epitopes that are for example, inaccessible in the non-wildtype conformation of a polypeptide. Accordingly, the particular target epitope is limited to epitopes in the chosen candidate polypeptide and the candidate polypeptides are limited to polypeptides that have different conformations (e.g. aggregated and non-aggregated). Similarly, the group of blocking agents and the group of detection agents are limited by the candidate polypeptide. A person skilled in the art would readily, based on the teaching in the application and prior art, be able to identify an appropriate detection agent and blocking agent for a given polypeptide that falls within the group of having a wildtype and non-wildtype conformation. For example, the application discloses a number of epitopes and detection agents in the table on page 39. If we take Tau as an example, which is listed in the aforementioned table, a person skilled in the art would know that the T14 antibody recognizes an epitope within amino acids 141-178 of human Tau. The skilled person could select a blocking agent that modifies amino acids within said region and would confirm that the epitope is a target epitope as described in the application. This is applicable to all of the many candidate polypeptides disclosed in the present application and to any polypeptide that exists in a wild type and non-type conformation. Accordingly, the instant specification in conjunction with the prior art provides sufficient guidance to enable a skilled artisan to practice the full scope of the claimed invention.

The Examiner also alleges that the instant specification fails to teach how to make and use all of the structurally and functionally undefined target epitopes, candidate polypeptides blocking agents and detection agents in the claimed method. However Applicant is not claiming "target epitopes, candidate polypeptides blocking agents and detection agents"; accordingly, Applicant is not required to teach how to make target epitopes, candidate polypeptides blocking agents and detection agents. MPEP §2164.01 provides that the test for enablement requires a

determination as to whether one of skill in the art can practice the *claimed* invention without undue experimentation. Here, Applicant is claiming a method, and the application provides a number of examples of how to use the method for a number of different candidate polypeptides, target epitopes, detection agents and binding agents and further teaches how to optimize the method and how to identify target epitopes. Accordingly, the methods as claimed are clearly enabled.

The Examiner alleges that it is known in the art that a single amino acid change can abolish the binding ability of a molecule and specifically refers to the loss of biological activity in FGF including the ability of heparin to bind to its receptor, occasioned by amino acid substitution. The Examiner further refers to an article by Pawson et al for the proposition that protein interactions also rely on flanking or noncontiguous residues. The relevance of these citations is not readily apparent to Applicant. Applicant is not claiming binding activities in the face of amino acid changes and Pawson et al refers to signaling pathways and describes the selective interactions between signaling molecules such as SH3. These papers are not relevant to the instant claims.

The Examiner further alleges "the instant specification fails to teach what structures/amino acid sequences can or cannot be included/changed in all candidate polypeptides to preserve an unknown wild type conformation and unknown target epitope. It is not readily apparent to Applicant what is meant by "changed to preserve an unknown wild type conformation". Applicant respectfully submits that there is no limitation to the polypeptide sequence per se. The limitation is that the candidate polypeptide must exist in a wild type and a non-wild type conformation. Whether the polypeptide has one or multiple mutations does not impact the application of the instant claimed methods. As claimed, the target epitope must be accessible in the wild type conformation and initially inaccessible in the non-wild type conformation.

In light of the above, Applicant respectfully submits that the specification discloses a number of methods for using the claimed invention that correlate to the entire scope of the claims

and respectfully requests that the objections to the claims under 35 USC §112 first paragraph for lack of enablement be withdrawn.

35 USC §112 first paragraph

The Examiner has rejected claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 as failing to comply with the written description requirement. For the reasons stated above, Applicant respectfully disagrees. As mentioned the specification provides numerous examples and teaches a number of candidate polypeptides, blocking agents, modifying steps and detection agents for use in the methods as previously described.

The Examiner also alleges that the rejected claims comprise "modifying the candidate polypeptide to an unknown mutant". The claims do not comprise modifying the candidate to an unknown mutant.

Also contrary to the Examiner's assertion, Applicant demonstrates more than prion PrP or PrP^{sc} epitopes recognized by antibodies 3F4 and 6H4, peroxynitrite as a blocking agent, guanidine to dissociate PrP and antibodies 3F4 and 6H4 as detection agents, as already discussed above. Further, guanidine is an example of a denaturing agent useful for many different protein aggregates. Other denaturing agents such as detergent and urea are well known in the art. Similarly, peroxynitrite chemically modifies amino acids such as tyrosine and is useful for chemically modifying many different proteins. Other chemical modifiers of amino acids are also known in the art.

Instead, the present invention teaches that one first treats the sample with a blocking agent, so that all exposed epitopes on the normal and disease forms of the target protein in the sample are blocked, and no longer bind to antibodies or other binding agents. If the target protein is present in an aggregated, disease form, then subsequent exposure to dissociating conditions will release component target proteins from the aggregate. Because the released component target proteins were insulated, by aggregation, from the blocking agent, they will present unblocked epitopes that are reactive with antibodies that bind the normal protein form. Thus, the presence of an aggregated form of a target protein in a given sample is revealed if, after

reaction with a blocking agent and subsequent dissociation, the sample tests positive with an antibody that normally binds that protein. If the aggregated form of the protein is not present in the sample, and the sample contains only the normal, non-aggregated form, the reaction with the blocking agent produces the normal protein in a form that cannot react with antibody normally reactive therewith, and subsequent dissociation and probing steps fail to produce a protein reactive with antibody probes. For proteins that present in aggregated form as a reflection of a disease state, the present method allows for detection of these aggregates to reveal the disease state, even if the normal non-aggregated protein is present in the sample at a detectable level.

Having illustrated the invention with reference to a target protein that, in a disease state, adopts an aggregated form, the specification teaches that epitope blocking provides an approach applicable for the detection of target proteins that, in the disease state, present with any conformation that is different from the normal conformation, provided there is at least one epitope that shifts between accessible and inaccessible states. Again, the blocking agent will mask the epitope if it is accessible, and will not mask the epitope if it is inaccessible. If the epitope is inaccessible to the blocking agent, then it will react with antibody probes when the sample is treated to shift the protein to the conformation in which the unreacted inaccessible epitope is then accessible to the antibody probe. When a sample is reactive with the antibody probe following exposure to the blocking agent, this indicates the sample comprises the target protein in an unusual, often disease-related, conformation.

The method, as recited in claim 1, is applied to detect whether a protein is in either a wild type or non-wild type conformation, that protein having a target epitope. According to the claim, a protein having an accessible target epitope is in a wild type conformation, whereas a protein having an inaccessible target epitope is in a non-wild type conformation (indicating a disease state, for example).

In light of the above, Applicant respectfully requests that the rejection to the claims for failing the written description requirement, be withdrawn.

Double patenting

The Examiner alleges that if claim 1 is found allowable, claim 39 will be objected to as being substantial duplicate thereof. Applicant respectfully disagrees. Claim 39 does not comprise contacting the polypeptide with a blocking agent. Having fewer steps, claim 39 is therefore distinct.

In light of the above, Applicant respectfully requests that this objection to claim 39 be withdrawn.

The Examiner has rejected claims 1, 2, 12 15-17, 20-22, 29-30, 39, 41, 47-49 and 51 on the ground of non-statutory obviousness type double patenting over claims 18-22 of U.S. Patent No. 7,041,807 (the '807 patent).

Applicant respectfully disagrees. Claims 18-22 of the '807 patent are not directed to an assay having a format like that presently claimed. Rather, these claims are directed to an antibody that binds selectively to one particular epitope of PrPSc, i.e., the YYR epitope. These claims do not include a step of using a blocking agent to mask epitopes present on proteins in a given sample, followed by dissociation and probing to detect PrPc. In fact, the antibody in these claims does not even bind PrPc – it binds selectively to the disease form of the prion protein, PrPSc, and thus would not be useful in the method presently claimed.

In light of the above Applicant respectfully requests that the double patenting rejections be withdrawn.

35 USC § 102

The Examiner has rejected claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 as being anticipated by U.S. Publication No. 2002/0123072 (the '072 publication) and U.S. Patent No. 6,677,125 (the '125 patent), both to Prusiner et al (collectively "Prusiner").

Applicant respectfully disagrees. None of the assays taught in the '072 publication or the '125 patent are encompassed by the claimed methods. Accordingly, the '072 publication and the

'125 patent do not anticipate the claimed methods. Because the '072 publication and the '125 patent contain the same disclosure, they are addressed together in the comments below. (All paragraph references are to the '072 publication).

Of the various assay formats suggested by Prusiner, one format uses proteases to digest a sample comprising both normal and aggregated (disease) forms of protein, such as the prion protein, PrP. For this protein, conventional nomenclature assigns PrPc to the normal protein, and PrPSc to the disease protein, which is an aggregated form of PrPc.

Prusiner suggests using the antibody 3F4 as a probe. This antibody binds to PrPc, but not the aggregated form, PrPSc. A sample containing PrPc will thus test positive for 3F4 immunoreactivity, as will as sample containing both PrPc and PrPSc. To make use of 3F4 as a probe for disease PrPSc, Prusiner suggests an initial step in which the sample (optionally pretreated to enrich for PrPSc) is hydrolyzed, for instance using an enzyme such as dispase. Provided the digestion reaction is very closely controlled, the enzymatic digestion will remove PrPc from the sample. Some of the PrPSc will also remain, provided the hydrolysis is not allowed to run to completion. The result is a sample that is no longer reactive with 3F4. Subsequent dissociation/denaturation results in exposure of component PrPc proteins within the PrPSc aggregate, and immunoreactivity with 3F4. Thus, a sample that tests positive for 3F4 after hydrolysis and dissociation is a sample presenting with the disease, PrPSc form of the prion protein, and indicates the sample source carries PrP infection.

The Prusiner assay relies absolutely on the carefully controlled digestion step. Indeed, according to Prusiner, "The hydrolysis treatment is a lytic treatment which is the most important treatment method used in one embodiment of the assays of the invention" (para [103]). "This treatment will destroy or hydrolyze all or substantially all protein in the sample which is in the non-disease conformation, and not hydrolyze the protein in the disease conformation" (para [103]).

No general hydrolysis reaction is able to achieve such selective results. Both PrPc and PrPSc are proteins vulnerable to hydrolysis, and since both comprise PrPc protein, both are

vulnerable to the same hydrolytic agent. What Prusiner essentially relies on is the difference in the rates at which, and the extents to which, the hydrolysis reaction will affect the different protein forms. PrPSc will degrade more slowly that PrPc, since the component PrPc within PrPSc are in aggregated form. Provided hydrolysis reaction conditions are carefully controlled, one can achieve the desired result in which all PrPc is hydrolyzed, yet some of the PrPSc remains. Prusiner identifies this desired result as "the object of the treatment is to hydrolyze as much non-disease protein as possible (preferably all) while hydrolyzing as little (preferably none) disease related protein as possible" (para [103]).

In order for the Prusiner assay to work, "the treatment is preferably designed such that it can be quickly and completely stopped at any given time". Clearly, it is not enough simply to digest the sample proteins – it is essential that control is exercised carefully over the digestion reaction.

The presently claimed assay offers a simple solution that addresses these difficulties. In the claimed assay, exposed surfaces on proteins in the sample are blocked by reaction with a blocking agent. With respect to PrP, one embodiment of the invention, this has the effect of blocking immunoreactivity with 3F4. The reaction can run to completion. There is no need or desire to reach a reaction mid-point that requires predetermination or monitoring in the sense required in the Prusiner assay, and subsequent timing to halt reaction progress. Exposing the treated sample to dissociation/denaturing conditions exposes unreacted PrPc, and 3F4 immunoreactivity then confirms the presence of PrPSc in the original sample.

The claimed assay is thus distinct from and not obvious from the assays described by Prusiner. As recited, claim 1 requires the step of contacting the polypeptide with a blocking agent, a step not performed or suggested by Prusiner. This step leaves the protein analytes intact, as distinct from the Prusiner approach of digesting the protein analytes in a manner necessarily controlled to preserve the target analyte. These steps are not interchangeable. One protects the target proteins while the other digests and eliminates them.

The Examiner has rejected claims 1-2, 9-17, 20-22, 29-30, 39, 41, 47-49 and 51 as being anticipated by U.S. Patent No. 7,041,807 (Cashman).

Applicant respectfully disagrees. There is no reference at all in Cashman to an assay having a format like that presently claimed. Cashman describes an antibody that binds selectively to one particular epitope of PrPSc, i.e., the YYR epitope. There is no description of an assay that comprises the step of using a blocking agent to mask epitopes present on proteins in a given sample, followed by dissociation and probing to detect PrPc. In fact, the Cashman antibody does not bind PrPc – it binds selectively to the disease form of the prion protein, PrPSc.

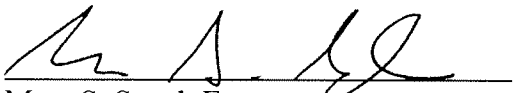
In light of the above, Applicant respectfully requests that the objections to the claims under 35 USC §102 be withdrawn.

In view of the foregoing, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, the Examiner is kindly requested to contact the undersigned.

No fee is believed to be due in connection with this submission. However, if a fee is due, the Commissioner is hereby authorized to charge any such fee or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

BALLARD SPAHR ANDREWS & INGERSOLL, LLP



Marc S. Segal, Esq.
Registration No. 40,163

BALLARD SPAHR ANDREWS & INGERSOLL, LLP
Customer Number 23859
(215) 864-8843 Phone
(678) 420-9301 Fax

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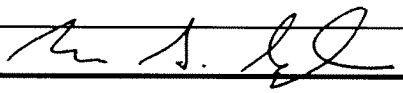
Signature		Date	3/23/2009